REMARKS

Applicants wish to thank Examiner Helms for the helpful telephonic interview with the undersigned on March 2, 2004. The substance of the interview pertained to the Non-Final Office Action mailed from the U.S. Patent and Trademark Office in the above-referenced patent application on September 3, 2003. Applicants also discussed a draft Amendment and Response, including an amended claim set, with the Examiner.

During the interview, Applicants proposed claim amendments to overcome the 35 U.S.C. §112, first paragraph rejection. In particular, Applicants proposed amendments to claim 56 to specify two types of constant region-mediated biological effector functions, *e.g.*, a protein having a reduced ability to activate complement or a reduced ability to bind to a Fc receptor. Applicants acknowledged that while the replacement of a single amino acid can, in some instances, result in alerted biological activity of the protein, as suggested by the Examiner in the Non-Final Office Action, the instant claims recite a functional limitation of the claimed composition. Thus, the assertion that "even a single amino acid substitution or what appears to be an inconsequential modification will often dramatically effect the biological activity of the protein" is not applicable to the pending claims, because the compositions are narrowly drawn to a modified fusion protein that retains a specific activity, *e.g.*, a protein having a reduced ability to activate complement or a reduced ability to bind to a Fc receptor.

Applicants further noted that the instant specification provides evidence of the ability to generate a functional CTLA4-Ig fusion protein which has mutations in the Ig constant region that eliminate Fc mediated function, and provides guidance as to how to generate such mutations and screen for mutants which possess the desired activity. Thus, the instant specification provides sufficient guidance to support the full breadth of the invention as claimed.

During the interview, the rejection of claims 56-59, 65-67, 69, 92 and 94 under 35 U.S.C. §103(a) as being unpatentable over Linsley *et al.* (U.S. Patent 5,434,131) and further in view of Gillies *et al.* (*Hum. Antibody.* Hybridomas 1:47-54, 1990) and Freeman *et al.* (U.S. Patent No. 6,130,316) and Canfield *et al.* (*J. Exp. Med.* 173:1483-1491, 1991) and Lund *et al.* (*J. of*

Immunol. 147:2657-2662, 1991) and Duncan *et al.* (*Nature* 332:738-740, 1988) were also discussed. In short, Applicants explained that Linsley *et al.* teaches that CTLA4 Ig is effective ***without*** any modifications to reduce complement activation and Fc receptor binding. The failure of the Linsley *et al.* reference to teach or suggest a critical element of the claimed ***modified*** CTLA4-immunoglobulin fusion protein, leads to a failure of the reference to teach or suggest the claimed compositions.

The remaining references fail to make up for this deficiency in the primary reference. Specifically, Freeman *et al.* does not teach or suggest modification of CTLA4-Ig fusion protein to reduce or eliminate Fc mediated receptor activity. A CTLA4-Ig fusion protein was previously known in the prior art to function absent such modification. In the absence of indications as to the particular benefit in making additional modifications, one of ordinary skill in the art would not have been motivated to apply the modifications to the Fc region of the cited prior art to the CTLA4-Ig fusion protein.

Furthermore, the specific advantage of reduced accumulation of the CTLA4-Ig fusion protein in the spleen, as indicated by the disclosure of Gillies *et al.*, is not of direct benefit in applications of the present invention. Absent teachings of a directly applicable benefit, one of ordinary skill in the art would not have been motivated by the disclosure of Gillies *et al.* to combine the teachings of the cited prior art to make the present invention.

Likewise, Canfield *et al.* and Lund *et al.* teach certain modifications to ***whole antibodies*** to examine the effect of amino acid substitutions on constant region mediated Fc receptor binding. These references fail to teach or suggest that such modifications could be made in ***any*** Ig fusion protein, let alone a CTLA4 Ig fusion protein. Moreover, the disclosures of Canfield *et al.*, Lund *et al.*, and Duncan *et al.* do not teach any benefits associated with eliminating Fc mediated responses in an antibody or an antibody fusion protein. Therefore, one of skill in the art would not have been motivated to combine the teachings of Freeman *et al.*, Gillies *et al.*, Canfield, *et al.*, Lund *et al.*, and Duncan *et al.* to produce the present invention.

Applicants agreed to summarize the foregoing arguments in the Amendment and Response to Non-Final Office Action filed with the U.S. Patent and Trademark Office on March 3, 2004.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. RPN-001CN from which the undersigned is authorized to draw.

Dated: April 5, 2004

Respectfully submitted,

By _____

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